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CuBr-mediated radical cascade difluoroacetamidation of acrylamides using α,α-difluoro-α-(TMS)-acetamides†

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Radical cascade difluoroacetamidation of *N*-(arylsulfonyl)acrylamides with α,α-difluoro-α-(TMS)-acetamides has been achieved for the first time. This CuBr-mediated transformation is easy to perform, generates high yields and shows a good substrate scope. This cascade reaction proceeds *via* difluoroacetamidation, aryl migration and desulfonylation. The products can be readily transformed into synthetically useful compounds such as difluorofunctionalized esters and alcohols in excellent yields.

Introduction

Incorporation of fluorine atoms into drugs often significantly improves their medicinal properties, such as lipophilicity and metabolic stability.[1] Among fluorine-containing groups, difluoromethylene (CF_2) has proven useful in drug development because it is a bioisostere that mimics the electronic features of an ethereal oxygen atom and because it acts as a lipophilic hydrogen-bond donor.[2] For instance, the difluorinated prostaglandin E1 analogue lubiprostone is an effective treatment for chronic idiopathic constipation,[3] and difluorostatone can act as an aspartic acid transition state inhibitor (Fig. 1).[4]

Therefore, methods to efficiently incorporate difluorinated moieties into diverse organic structures are desirable. Various difluoromethylating reagents have been developed,[5–12] but the resulting difluoromethylated products are difficult to derivatize further.[19e] In contrast, the novel radical difluoromethylating reagent α,α-difluoro-α-(TMS)-acetamide generates difluoroacetamidated products that can be conveniently converted to other useful moieties, such as difluoroacetate ($-CF_2COOR$) and difluoroethanol ($-CF_2CH_2OH$).[13b] In addition, this difluoromethylating reagent is easily mediated in the reactions using inexpensive metals. While this reagent has been used in the coupling with aryl halides or direct addition to alkene derivatives,[13] we are not aware that it has been applied to the cascade difunctionalization of alkenes, which is quite attractive for its ability to construct two vicinal bonds in a single step.[14,15]

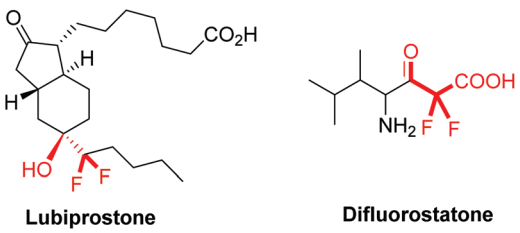

Fig. 1 Drugs containing the difluoro moiety.

One of the most efficient strategies for the difunctionalization of alkenes is a cascade protocol involving radical addition and intramolecular rearrangement.[16] In 2013, the Nevado group reported a novel radical cascade involving *N*-(arylsulfonyl)acrylamides, which proceeded *via* aryltrifluoromethylation, aryl migration and desulfonylation.[17a] Subsequently, several groups developed protocols for radical arylphosphonylation, arylazidation, arylalkylation, aryltrifluoromethylation, and diarylation of phenylsulfonyl acrylamide.[18–20] However, the radical aryldifluoroacetamidation of phenylsulfonyl acrylamide does not seem to have been reported.

As part of our continuing efforts to introduce fluorine-containing groups into alkene derivatives,[21] we report here a novel radical cascade difluoroacetamidation of *N*-(arylsulfonyl)acrylamides involving difluoromethylation, aryl migration and desulfonylation. The difluoroacetamidated product was readily transformed into the corresponding difluorofunctionalized esters and alcohols in good yields.

We began investigating this radical cascade reaction using *N*-(arylsulfonyl)acrylamide **1a** and *N*,*N*-diethyl-α,α-difluoro-α-(TMS)-acetamide **2a** as model substrates in the presence of a

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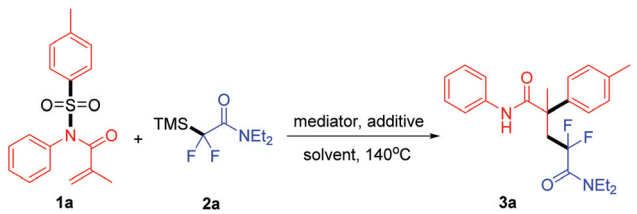
metal mediator (2 equiv.) at 140 °C under N_2 (Table 1). Screening of Fe, Ag and Cu mediators (entries 1–8) showed that AgOAc performed well, generating the desired product in 56% yield (entry 3), while better yields were obtained with CuBr (79%, entry 7) and CuCl (75%, entry 8). The amount of CuBr could be reduced to 1.5 equiv. with only a slight decrease in yield (entry 9). Solvents DMF and DMSO did not perform as well as CH_3CN (entries 10 and 11). Lowering the reaction temperature significantly decreased the yield of **3a** (entry 12), and adding an acid to the system completely blocked the reaction (entries 13 and 14). Phenanthroline and bipyridine, despite being efficient ligands in many other Cu-catalyzed transformations, did not give satisfactory results (entries 15 and 16), nor did the frequently used bases CsF, Na_2CO_3, pyridine or NEt_2 (entries 17–20). The combination of a catalytic amount of CuBr (0.2 equiv.) and oxidants such as Selectfluor, $K_2S_2O_8$ or $Mn(OAc)_3$, did not improve the yield (entries 21–23).

Using these optimized conditions (entry 9, Table 1), we examined the substrate scope of the cascade reaction (Table 2). Various *N*-(arylsulfonyl)acrylamides reacted with *N*,*N*-diethyl-α,α-difluoro-α-(TMS)-acetamide to give the corresponding products **3a–3q** in moderate to good yields. *N*-(Arylsulfonyl)acrylamides substituted at the *para* position with electron-donating substituents (–OMe, –Me, *t*-Bu) reacted smoothly to afford the desired products **3b–3d** in 81–83% yields. The substrate substituted at the *para* position with a Ph gave the target product **3e** in 77% yield. Substrates with electron-withdrawing groups (–Cl, –Br) at the same position slightly improved the reaction, affording products **3f–3g** in excellent 84–85% yields. Interestingly, acrylamides substituted at the *meta* position with –OMe, –Me, –Cl or –Br participated in the reaction, delivering the target products **3h–3k** in 79–88% yields. Similarly, acrylamides substituted at the *ortho* position with –OMe, –Me, or

Table 1 Optimization of the conditions for reactions of **1a** and **2a** [a]

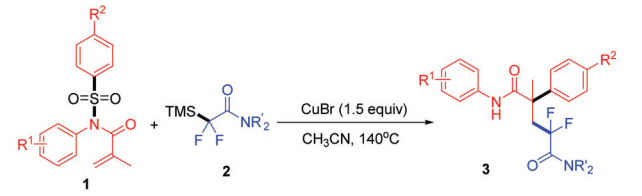


1a 2a 3a

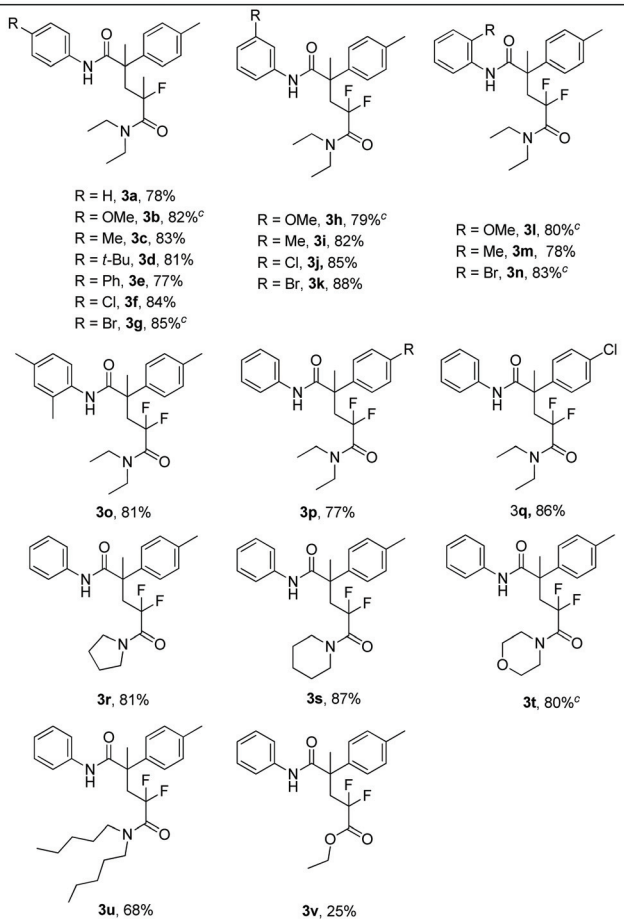
Entry	Mediator	Additive	Solvent	Yield[b]
1	$FeCl_3$	None	CH_3CN	N.D.
2	$AgNO_3$	None	CH_3CN	22%
3	AgOAc	None	CH_3CN	56%
4	$Cu(OAc)_2$	None	CH_3CN	30%
5	$CuBr_2$	None	CH_3CN	15%
6	$CuSO_4$	None	CH_3CN	23%
7	CuBr	None	CH_3CN	79%
8	CuCl	None	CH_3CN	75%
9[c]	CuBr	None	CH_3CN	78%
10[c]	CuBr	None	DMSO	25%
11[c]	CuBr	None	DMF	40%
12[c,d]	CuBr	None	CH_3CN	26%
13[c]	CuBr	MesCOOH	CH_3CN	Trace
14[c]	CuBr	PivOH	CH_3CN	Trace
15[c]	CuBr	Phenanthroline	CH_3CN	22%
16[c]	CuBr	Bipyridine	CH_3CN	27%
17[c]	CuBr	CsF	CH_3CN	48%
18[c]	CuBr	Na_2CO_3	CH_3CN	33%
19[c]	CuBr	Pyridine	CH_3CN	38%
20[c]	CuBr	NEt_2	CH_3CN	46%
21[e]	CuBr	Selectfluor	CH_3CN	Trace
22[e]	CuBr	$K_2S_2O_8$	CH_3CN	23%
23[e]	CuBr	$Mn(OAc)_3$	CH_3CN	N.D.

[a] Reaction conditions: Reactions were performed in sealed tubes containing **1a** (0.2 mmol), **2a** (2 equiv.), mediator (2 equiv.), additive (2 equiv.) and solvent (2 mL) under N_2 at 140 °C. N.D. = not detected. [b] Isolated yield. [c] CuBr (1.5 equiv.) was used. [d] Temperature was 100 °C. [e] CuBr (0.2 equiv.) was used.

Table 2 Reaction of various *N*-(arylsulfonyl)acrylamides **1** and α,α-difluoro-α-(TMS)-acetamides **2** [a,b]



1 2 3



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), CuBr (0.3 mmol), CH_3CN (2 mL), 140 °C, 6 h, under N_2. [b] Isolated yield. [c] Reaction time was 9 h.

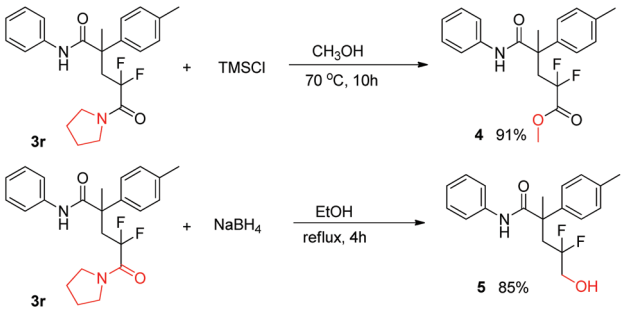
–Br provided the desired products **3l–3n** in 78–83% yield. Dimethyl-substituted acrylamide reacted efficiently with **2a**, affording product **3o** in 81% yield.

Next we investigated the effects of substituents on the phenysulfonyl ring. Good results were obtained with electron-withdrawing and -donating substituents. In fact, electron-withdrawing groups slightly improved the yield (**3p–3q**). The molecular structure of **3p** was unambiguously confirmed by X-ray diffraction analysis (Fig. 2).

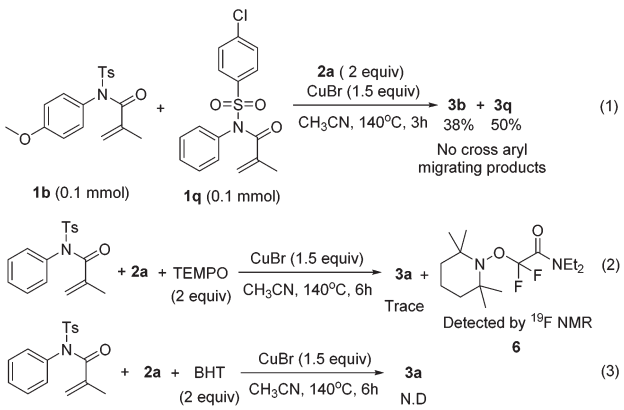
We then evaluated the reactivities of *N*-(arylsulfonyl)acrylamide **1a** with different α,α-difluoro-α-(TMS)-acetamides **2** under optimized conditions. To our delight, the reaction between cyclic amides and *N*-(arylsulfonyl)acrylamide **1a** furnished the difluoroacetamidated alkenes **3r–3t** in good to excellent yields. Nevertheless, *N*,*N*-diamylacetamide showed lower reactivity, providing the corresponding product **3u** in moderate 68% yield. Besides, the α,α-difluoro-α-(TMS)-acetate was also compatible in the reaction and furnished product **3v** in 25% yield. When substrates **2** with an allyl group or benzyl group as R′ were applied to this reaction, complicated products were generated but no disired products **3** were observed.

To demonstrate the synthetic potential of this methodology, we performed several derivatizations of product **3r**. Given that the two fluorine atoms on the α-carbon of the amide should increase autologous electrophilicity, we predicted that the alkylamide moiety could be easily transformed into various functional groups, while leaving the phenylamide moiety untouched. When the difluoroamidated product **3r** was treated with TMSCl, the difluorofunctionalized ester **4** was obtained in excellent 91% yield (Scheme 1). When the difluoroamidated product **3r** was treated with sodium borohydride, it was smoothly reduced to the corresponding alcohol **5** in 85% yield (Scheme 1).

To gain insight into the mechanism of this radical cascade reaction, we conducted several control experiments (Scheme 1). When two acryl sulfonamides **1b** and **1q** were reacted with **2a** under standard conditions, no cross aryl-migrating products were obtained (eqn (1), Scheme 2). These results demonstrate that 1,4-aryl migration proceeds *via* an intramolecular process. Adding the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) to the reaction under standard conditions led to only trace amounts of the desired



Scheme 1 Derivatization of product **3r**.



Scheme 2 Mechanistic studies of the cascade reaction.

product **3a**. In addition, the radical trapping product **6** was detected in the reaction (eqn (2), Scheme 2; see the ESI†). The reaction was completely blocked when the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the system. These results suggest that the reaction involves a radical process, and that the difluoroacetamide radical may participate in this reaction.

Based on these experimental results and the related studies on aryl migration and Smiles rearrangement,[17,22,23] we propose a mechanism for the radical cascade reaction

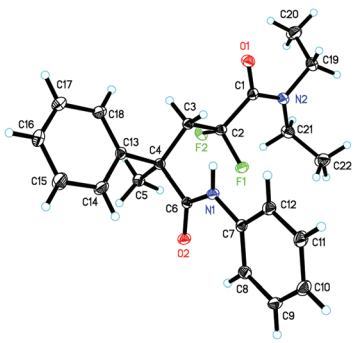
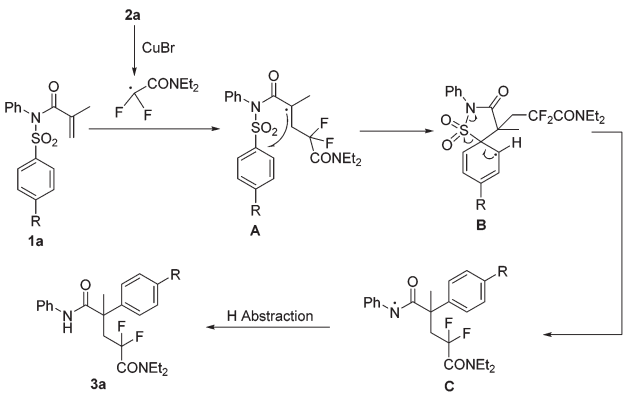


Fig. 2 X-ray crystal structure of **3p**.



Scheme 3 Plausible mechanism of the cascade reaction.

(Scheme 3). Initially, a difluoroacetamide radical is generated from **2a** in the presence of CuBr.[13] This radical adds to the C=C bond of **1a**, affording radical intermediate **A**, which undergoes 5-*ipso*-cyclization on the aromatic ring to generate intermediate **B**. Rapid desulfonylation affords the key amidyl radical intermediate **C**, which abstracts a hydrogen atom to give the target product **3a**.

Conclusions

In summary, we have developed a new radical cascade protocol to difunctionalize *N*-(arylsulfonyl)acrylamides using α,α-difluoro-α-(TMS)-acetamides. This straightforward transformation allows the synthesis of various amides with all-α-carbon quaternary stereocenters. It proceeds *via* difluoroacetamidation, aryl migration and desulfonylation. The products can be readily transformed into difluorofunctionalized alcohols and esters in excellent yields. This efficient protocol may be applied as a useful method for drug development and natural product synthesis.

Acknowledgements

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